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10/695,247	10/27/2003	Wayne Dawson	F-8015	5890

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EXAMINER	
SKOWRONEK, KARLHEINZ R	

ART UNIT	PAPER NUMBER
1631	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/695,247	Applicant(s) DAWSON ET AL.	
	Examiner KARLHEINZ R. SKOWRONEK	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-9 and 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

Claim Status

Claims 2-9 and 11 are pending.

Claims 1, 10, and 12-13 are cancelled.

Claims 2-9 and 11 are being examined.

Claims 2-9 and 11 are rejected.

Election/Restrictions

Upon reconsideration of the restriction requirement of 26 May 2006, the requirement for restriction is withdrawn.

Claim Rejections - 35 USC § 112, 2nd Paragraph
Response to Arguments

The rejection of claims 2-7 as indefinite reciting “as rapidly as” under 35 USC 112, second paragraph are withdrawn in view of the amendment to the claims

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following rejection is reiterated from the previous action.

Claims 2-7 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2 and 7 are also unclear with respect to the equation C(n+1)(n-1). The metes and bounds of the claim are unclear. The variable “C" is defined to be any

constant. In the trivial case, this could be zero. In that case, the equation evaluates to zero and has no effect. The claim refers to polynomial time, however the equation does not provide a variable representation of time. The art uses the term “polynomial time” algorithms to describe the amount of computation time required to solve the problem grows no faster than some fixed power of the problem size, e.g., the number of cities in the traveling salesman problem (Bryngleson et al. (PROTEINS: Structure, Function, and Genetics 21:167-195 (1995)) p. 170, col. 2). In the instant claim, it is unclear if the equation describes a polynomial time algorithm. The rejection could be overcome by amendment of claims 2 and 7 from " polynomial time: c(n+1)(n-1)” to polynomial time defined by c(n+1)(n-1)”. Claims 3-6 are also rejected because they depend from claim 2, and thus contain the above issues due to said dependence.

Response to Arguments

Applicant's arguments filed 08 March 2010 have been fully considered but they are not persuasive. Applicant argues that the constant refers to the software implementation issues. The argument is not persuasive. The claims do not reflect that the constant is related to software implementation issues. While the claims are read in view of the teachings of the specification, limitations from the specification are not read into the claims.

Claim 9 is unclear with respect to the integral shown in equation (3). The integral is bounded from +1 to ξ. The claim recites that x is dummy variable substituting for ξ. It is unclear what ξ is. If ξ is being represented by x, it appears the integral should be

evaluated over the range of +1 to x and x should replace all instances of ξ. Alternatively, all instances of x should be replaced by ξ. Thus, it is unclear what applicant intends by redefining ξ which in turn makes it unclear what ξ is. This rejection could be overcome by amending claim 9 at line 44 to recite “x is a variable in the integral for values in the range from 1 to ξ”.

Response to Arguments

Applicant's arguments filed 08 March 2010 have been fully considered but they are not persuasive. Applicant argues the meaning of the variable “ξ” is clear in context of the claim and do not redefine the variable as the dummy variable “x”. The argument is not persuasive. While the claim does properly define the variable the claim also confusingly refers to the variable as substituted by the dummy variable “x”. The multiple references make the meaning of the variables unclear. As suggested above, the rejection of claim 9 could be overcome by clarifying “x is a variable in the integral for values in the range from 1 to ξ”.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejection is reiterated from the previous action.

Claim 8 and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Floudas et al. (USPAT 6,832,162) in view of Alm et al. (Proc. Natl. Acad. Sci., Vol. 96, p.11305-11310, September 1999), in view of Dawson et al. and in view of Turner (US Pat 5,424,963).

The claims are drawn to a method that uses an entropy evaluation model combined with other thermodynamic potentials as a protein-folding model to predict

topology. In some embodiments, the entropy model is used to evaluate the loss in entropy due to folding into a particular topology. In some embodiments, the method involves the steps of inputting an amino acid sequence; preparing secondary structure information; applying the model to evaluate free energy; applying the model in conjunction with other thermodynamic parameters; predicting folding kinetics; and storing the data.

Floudas et al. teach a method of predicting protein topologies. Floudas et al. show that a global entropy model is used to evaluate the folding of a protein (col 15, eq. 8). In some embodiments, Floudas et al. teach the initial estimate is calculated from the experimental sources (col. 9, line 39-52). In some embodiments, sequence alignment is used to supplement the estimate (col 10, line 1-12). In some embodiments the method involves the steps of inputting an amino acid sequence (fig. 2 and col 11, line 20-24); preparing secondary structure information (col. 11, line 2-5); applying the model to evaluate free energy (col 11, line 27-29); applying the model in conjunction with other thermodynamic parameters (col. 13, line 25-30). In some embodiments, Floudas et al. show evaluations are made in polynomial time (col 10. line 19-21).

Floudas et al. do not show predicting folding kinetics and storing the data.

Alm et al. show a method for predicting protein folding using native-state topology. Alm et al. show that an entropy evaluation model that accounts for the global contributions to entropy is used (p. 11307, col. 2). Alm et al. show the prediction of protein topologies (fig. 3). In some embodiments, Alm et al. teach the entropy model is used to evaluate the loss in entropy due to folding into a particular topology (p. 11306,

col.1). In some embodiments, Alm et al. show the initial estimate is calculated from the experimental sources that are derived from x-ray crystallography (p. 11306, col. 1). In some embodiments, Alm et al. show that folding kinetics is predicted (p. 11306, col. 1). In some embodiments, Alm et al. show that the information is stored (fig 1 and p. 11306, col. 2). Alm et al. shows that a simple treatment of the interactions in a native protein is sufficient to account for most of the experimental data available on the folding of small protein domains (p. 11305, col. 2).

Dawson et al. show a method for calculating Cross Linking Entropy of biopolymers. Dawson et al. use nucleic acids as an exemplary demonstration of the global strategy for estimating entropy. Although, the method is mostly directed to nucleic acids Dawson suggest that the calculation can be applied to proteins and to the evaluation of free energy in protein folding (p.377, col. 2). Dawson et al. show teach the equation $\Delta S_{i,j} = \frac{\gamma k_B}{\xi}\left[\ln\left(\frac{2\gamma\xi N_{i,j}}{3\lambda^2}\right) - 1 + \left(\frac{3\lambda^2}{2\gamma\xi N_{i,j}}\right)\right]$ (p.368, eqn 9), after the terms θ(ξ)= $\frac{1}{\xi}$ (eqn. 8) and $\psi = \frac{2\gamma\xi}{3\lambda^2}$ are substituted into Eqn. 9. Further, it is well known in the art that $\Delta G = \Delta H - T\Delta S$ and Dawson et al. teach that the calculation total Gibb's free energy (p. 370, eqn. 16). Dawson et al. teach the entropy calculation makes the correct predictions about the direction of folding in a biopolymer such as proteins (p. 378, col. 2).

Floudas et al., in view of Alm et al., in view of Dawson et al. do not show polynomial time.

Turner et al shows a method of predicting protein folding in which the evaluation of a combinatorial number of secondary structural element arrangements is determined in polynomial time defined by o(n2) (col. 7, line 44-46). Turner et al shows proteins can be partitioned into bodies that define secondary structure elements (col. 9, line 61-66). Turner shows the method of partitioning provides benefits which include significant reduction in the number of degrees of freedom (DOF) that must be retained in the model and simplification of the potential surface, thereby allowing more rapid exploration of the phase space motions (col. 7, line 39-43).

It would have been obvious for one of skill in the art at the time the invention was made to modify the method of Floudas et al. for predicting tertiary protein structures and topology with the method of Alm et al. for predicting protein folding from free energy landscapes because Alm et al. shows that a simple treatment of the interactions in a native protein is sufficient to account for most of the experimental data available on the folding of small protein domains. It would have been further obvious to one of ordinary skill in the art to modify the method for predicting tertiary protein structures of Floudas et al in view of Alm et al. with the multi-body techniques of Turner et al because Turner et al shows the method of partitioning into bodies provides benefits which include significant reduction in the number of degrees of freedom (DOF) that must be retained in the model and simplification of the potential surface, thereby allowing more rapid exploration of the phase space motions. This is an advantage because it simplifies the computation. It would have been further obvious to one of ordinary skill in the art at the ;time of invention to modify the method for predicting tertiary protein structures of

Floudas et al in view of Alm et al. with the entropy calculations of Dawson et al. because Dawson et al shows the entropy calculation makes the correct predictions about the direction of folding in a biopolymer such as proteins.

Response to Arguments

Applicant's arguments filed 08 March 2010 have been fully considered but they are not persuasive. Applicant argues the combination of Floudas et al., Alm et al., Dawson et al., and Turner et al fail to show the evaluation of the free energy of a combinatorial number of secondary structure arrangements performed in polynomial time. The argument is not persuasive. Claim 8 does not require the evaluation of the free energy of a combinatorial number of secondary structure arrangements performed in polynomial time. Applicant argues that the combination of Floudas et al., Alm et al., Dawson et al., and Turner et al fail to show equation 3 and the element of equation 2, the $f_{i'j'}(\xi)$ penalty function. The argument is not persuasive because claim 8 does not recite either equation 3 or the element of equation 2, the $f_{i'j'}(\xi)$ penalty function.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to KARLHEINZ R. SKOWRONEK whose telephone number is (571)272-9047. The examiner can normally be reached on 8:00am-5:00pm Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/KARLHEINZ R SKOWRONEK/
Primary Examiner, Art Unit 1631

15 July 2010